AMNIOTIC FLUID UREA NITROGEN, URIC ACID, AND CREATININE IN DIABETIC PREGNANCIES*

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PREGNANCIES complicated by maternal diabetes are associated with high perinatal mortality. Fetal salvage in these pregnancies can be improved by premature delivery, but selection of the optimal time to interrupt gestation has been based on poorly defined considerations, such as degree of fetal activity, reduction in insulin requirements, failure of toxemic symptoms to respond to treatment, decreased rate of fetal growth, and perhaps urinary estriol levels.[1]

Investigation of the amniotic fluid constituents in pregnancy complicated by maternal diabetes followed results of studies in fetal erythroblastosis, where improved management of hemolytic fetal disease arising from maternal Rh antibodies has been achieved by using the concentration of amniotic fluid constituents as a guide for treatment.[2] With development of this new interest in the amniotic fluid compartment as a mirror of fetal health, urea, creatinine, and uric acid were studied in diabetic pregnancies. These fetal waste products are excreted

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TABLE I. SUMMARY OF OBSERVATIONS OF URIC ACID, UREA NITROGEN, AND CREATININE

Patients	*Number*		*Uric acid*			*Urea nitrogen*			*Creatinine*		
			A. F. mg. %	*Mat. ser.* mg. %	*Ratio*	*A. F.* mg. %	*M. S.* mg. %	*Ratio*	*A. F.* mg. %	*M.S.* mg. %	*Ratio*
Normals	18	Mean	5.8	3.6	1.6	12.9	8.0	1.6	1.9	0.7	2.7
		S.D.	± 1.2	±0.5	±0.4	± 5.0	± 3.1	±0.4	±1.5	±0.3	±1.7
		Med.	5.9	3.6		12.7	8.2		1.7	0.6	
Rh	24	Mean	6.4	4.0	1.6	12.4	7.8	1.6	1.5	0.6	2.5
		S.D.	± 2.1	±0.7	±0.5	± 4.2	± 2.1	±0.5	±0.3	±0.2	±0.6
		Med.	6.6	4.2		12.2	7.9		1.3	0.5	
Diabetics											
Class A	3	Mean	5.5	4.0	1.4	18.0	11.2	1.6	1.9	0.6	3.1
		S.D.	± 1.9	±1.0	±0.3	± 8.0	± 3.2	±0.5	±0.7	±0.2	±0.3
		Med.	8.0	4.2		22.0	10.5		1.9	0.7	
Class B	5	Mean	9.8	6.5	1.5	14.0	9.4	1.5	2.2	0.9	2.4
		S.D.	± 3.4	±2.4	±0.6	± 3.1	± 2.0	±0.4	±0.6	±0.2	±0.6
		Med.	8.8	6.7		13.0	8.9		2.1	0.8	
Classes C & D	12	Mean	10.6*	6.6*	1.6	20.0*	15.0*	1.3	2.1	1.4*	1.9*
		S.D.	± 2.7	±1.7	±0.4	± 6.0	± 3.5	±0.7	±0.6	±0.3	±0.6
		Med.	9.7	6.4		20.0	14.5		2.0	1.2	
Normal values from literature (R)			4.9			14.5		1.4	1.8		2.9 ±0.8

* Significant difference by t-test when compared to normals ($p < 0.05$)

TABLE II. COMPARISON OF CREATININE CONTENT

(Mg. %)	
Cord blood	*Maternal blood*
5.6	5.4
0.9	1.0
2.0	1.0
2.7	2.6
1.1	0.8
0.9	0.7
0.9	0.8
0.9	1.0
1.1	1.0
1.2	1.3
0.9	0.9
0.9	0.8

in high concentration in fetal urine, and fetal urine contributes significantly to the formation of amniotic fluid in the third trimester. This is a preliminary report of these studies.

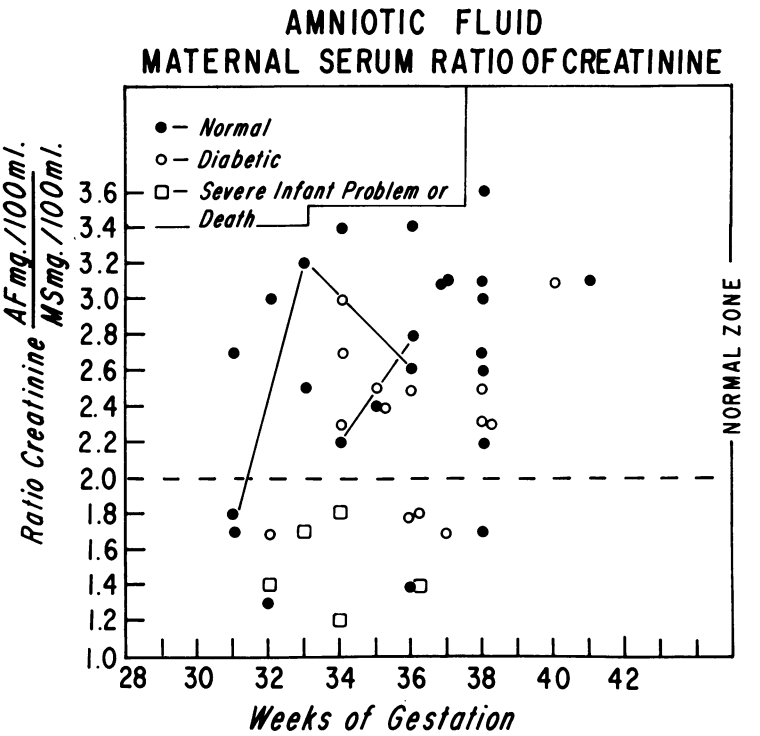
MATERIALS AND METHODS

Sixty-two specimens of amniotic fluid were obtained by transabdominal amniocentesis from 18 normal women, 24 Rh-immunized women, and 20 diabetics. Venous blood was drawn at the same time, and cord blood was obtained when possible at delivery. All patients were followed in the prenatal clinics of The Mount Sinai Hospital. Diabetic patients were classified according to Priscilla White.[1] Specimens from patients were obtained at the time of cesarean section or by serial amniocentesis. The method of amniocentesis is outlined elsewhere.[2] Microchemical determinations of uric acid, urea nitrogen and creatinine were performed by routine methods.[4, 5]

RESULTS

Amniotic fluid values. Table I gives the mean, its standard deviation, and the median amniotic fluid concentration values for uric acid, urea nitrogen and creatinine by category of case. A significant elevation of the mean values for the concentration of urea nitrogen and uric acid is to be noted for the class *C* and *D* diabetics.

Maternal serum values. The mean maternal serum levels of creati-



Figure

nine, uric acid, and urea for class *C* and *D* diabetes are shown in Table I to be significantly elevated ($p < 0.05$).

Amniotic fluid maternal blood ratios. Table I includes a comparison of the ratio of the concentration of urea nitrogen, uric acid, and creatinine in amniotic fluid and in maternal serum. These values were derived simply by dividing the concentration in amniotic fluid (mg./100 ml.) by the concentration of the same material in maternal serum. In diabetics a normal concentration ratio of about 1.6 was encountered for both uric acid and urea nitrogen. For creatinine, however, a significantly decreased ratio was found in these patients. The ratios, or gradients, for creatinine and urea nitrogen in normal patients are similar to those reported by McGaughey.[6] The ratio of creatinine for normal patients was 2.7 ± 1.7 but the ratio for class *C* and *D* diabetics was 1.9 ± 0.8, a statistically significant difference ($p < 0.05$).

Comparison of cord blood with maternal blood values. Table II

TABLE III

Case	Clinical data	Weeks of amniocentesis	Creatinine A.F. (mg. %)	Creatinine M.S. (mg. %)	Creatinine Ratio {A.F.}{M.S.}
C.R.	Class *D* diabetic 35 weeks stillborn	34	1.7	1.4	1.2
F.D.	Class *C* diabetic, infant with severe respiratory distress and hypoglycemia at 36 weeks	34	1.4	0.8	1.8
D.M.	Class *A* diabetic, with severe toxemia. Infant had respiratory distress, moderate degree at 38 weeks	36	1.5	1.1	1.4
R.R.	Class *A* diabetic with severe toxemia and chronic renal disease. Infant had respiratory distress, severe. Placental infarctions at 38 weeks	33	4.3	2.6	1.7
D.D.	Class *B* diabetic hypertensive with fetal death within 24 hours from respiratory distress syndrome at 36 weeks	32	1.6	1.1	1.4

compares the levels of creatinine in 12 paired sera from cord blood and from maternal blood. Little variation was observed between the pairs; this confirmed previous reports.[6]

Clinical correlations. The figure shows the amniotic fluid/maternal serum ratio of creatinine for all cases in relation to stage of gestation. At 33 weeks or later in pregnancy only three of 19 normal patients fall below the 2.0 level. In contrast, half of the diabetic mothers are in this group and—of particular interest—five of the nine infants of these diabetics had severe neonatal complications or perinatal deaths. Table III summarizes the data in these five cases.

DISCUSSION

Urea, creatinine, and uric acid are fetal waste products excreted in fetal urine in concentrations higher than those in fetal or maternal blood. Fetal urine is markedly hypotonic when compared to either maternal or fetal plasma. Thus the increase in amniotic fluid concentrations of these constituents and the decrease in total solute concentration during the last part of pregnancy indicate a significant contribution to this fluid space by fetal urine.[3]

Creatinine, urea, and uric acid have been shown[7] to be present in amniotic fluid in increased concentration relative to that found in the maternal serum even though both urea and creatinine readily permeate the placental membranes. These concentration gradients have been attributed to the high rate of deposition of the products into the fluid, coupled with diffusion characteristics of the chorioamnion. Existing evidence suggests that the chorioamnion has a limited capacity for diffusion, thus preventing equilibration. An active secretory process into the fluid across these membranes has been ruled out as an explanation of these gradients.[6]

Elevated levels of urea and uric acid have been demonstrated in amniotic fluids of diabetic mothers. This is likely to reflect increased fetal urinary output of these substances, but a comparison of the concentration gradients between amniotic fluid and maternal serum revealed no alteration from the normal. Thus the elevation of uric acid and urea nitrogen in the fluid can best be explained by increased urinary excretion secondary to elevated fetal blood levels. The levels of these nonprotein nitrogenous materials in fetal bloods are in equilibrium across the placenta, and they reflect elevated maternal levels; the substances are excreted in higher amounts in the fetal urine.

The creatinine gradient between amniotic fluid and maternal serum may not be maintained in some cases. One possible explanation for this fact would be decreased fetal urinary output of creatinine despite elevated maternal and fetal concentrations. Creatinine output is one of the more sensitive indicators of urinary functions, namely glomerular filtration.[8] Perhaps the fetal glomerular filtration rate is diminished in the presence of severe maternal diabetes. It is of interest that edema of the fetal nephrons has been reported in fetal deaths associated with maternal diabetes,[9] and that decreased amniotic fluid creatinine has also been reported in association with maternal toxemia.[10] However, Osler has found that the glomerular filtration rate in newborn infants of diabetic mothers was of the same magnitude as that in normal infants.[11]

Another explanation for these observations might be intrauterine fetal diuresis, resulting in polyhydraminos and a fall in creatinine concentration. Maintenance of the urea and uric acid content of the amniotic fluid would then reflect increased fetal excretion of these products. Osler has reported an increased excretion of water per unit of nitrogen during the first 24 hours of life in infants born to diabetic

mothers.[11] Other investigators have also noted the diuresis and hemoconcentration associated with these infants.[12,13]

The mechanism and specificity of these changes for diabetic pregnancies and their use as indicators for clinical management are under investigation.

Summary

The nonprotein nitrogen constituents of amniotic fluid and maternal blood in normal pregnancies and those complicated by maternal Rh incompatibility and diabetes were studied by the use of antepartum amniocentesis. Significant elevation in the urea nitrogen and uric acid content of the fluids from diabetic pregnancies occurs; however, the maternal levels were elevated proportionally, so that the amniotic fluid/maternal serum gradient was unchanged. The normal amniotic fluid/maternal serum gradient for creatinine was decreased for class *C* and *D* diabetes from approximately 3:1 to 2:1 despite elevated maternal serum levels. The decreased creatinine gradient was often associated with fetal perinatal mortality and morbidity. The possible etiology of these alterations is discussed.

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